REMARKS

Applicants have carefully studied the Final Office Action mailed July 12, 2011, which issued in connection with the above-identified patent application.

The present response is intended to be fully responsive to all points raised by the Examiner in the July 12, 2011 Final Office Action and is believed to place the claims in condition for allowance. Favorable consideration and allowance of the present claims are respectfully requested.

I. Pending Claims

Claims 1, 3, 4, 9-13, 15-20, 22, 23, 28-31, 33-37, 40, 45, 46, 51-53 and 56 were pending in this application, with Claims 11-13, 15-19, 29-31, 33-37, and 40 having been previously withdrawn from consideration as directed to non-elected subject matter.

Claims 1, 3, 4, 9-13, 15-19, 40 and 56 are presently canceled without admission and without prejudice or disclaimer. Applicants preserve the right to pursue the subject matter of those canceled claims in divisional and/or continuation applications. Claim 20 has been amended to recite an "immunogenic composition," and to recite that the composition "is suitable for mucosal administration and, when administered mucosally to a mammal expressing an endogenous prion protein, elicits a primarily Th-2-type immune response against said endogenous prion protein of said mammal." Support for these amendments can be found, e.g., at page 10, first full paragraph; page 14, first full paragraph; page 15, first paragraph; and at page 20, last paragraph of the present application.

Claims 22, 28-31, 33-37 and 45 have been amended to increase clarity.

Claim 53 has been amended to correct dependency.

New Claim 57 has been added. Claim 57 recites the composition of Claim 20, further comprising aluminum hydroxide. Support for new Claim 57 can be found, for example, at page 8, third full paragraph, and page 9, last paragraph of the application.

No new matter has been added by way of these amendments.

Upon entry of these amendments, Claims 20, 22, 23, 28, 45, 46, 51-53 and 57 will be under consideration.

II. Structural and Functional Limitations of the Present Claims

In the Office Action (see, e.g., page 7), the Examiner asserts that the present claims do not recite any structural components of compositions for mucosal administration. Applicants respectfully note that all presently pending claims recite immunogenic compositions comprising an attenuated bacterium microorganism consisting of one of a *Shigella* strain and a *Salmonella* strain transformed with a vector capable of expressing a non-infectious, non-pathogenic mammalian prion protein selected from the group consisting of mouse, bovine, deer, elk, and sheep prion protein. These are all structural limitations.

The present claims also contain two functional limitations: (1) suitable for mucosal administration and (2) elicits a primarily Th-2-type immune response against said endogenous prion protein that is associated with a mucosal IgA humoral immune response and any concomitant immunoglobulin counterpart in other bodily fluids, and is not associated with a primarily Th-1-type cytotoxic T-lymphocyte response.

The Examiner has acknowledged that the limitation (1) is a true claim limitation, but argues that the limitation (2) is an intended use, which does not further limit the claims. Applicants respectfully disagree.

As specified in MPEP 2173.05(g), "There is nothing inherently wrong with defining some part of an invention in functional terms. Functional language does not, in and of itself, render a claim improper. *In re Swinehart*, 439 F.2d 210, 169 USPQ 226 (CCPA 1971). A

functional limitation must be evaluated and considered, just like any other limitation of the claim, for what it fairly conveys to a person of ordinary skill in the pertinent art in the context in which it is used."

The Examiner also questions whether the claimed compositions possess the functional property (2).

In response, Applicants respectfully note that the present application demonstrates that immunization with the claimed composition (specifically, *Salmonella typhimurium* strain LVR01 containing the mouse PrP cDNA) increases survival of mice following prion infection (see, e.g., Example 4, pages 33-34 of the present specification, and Figures 2 and 3). See also more detailed immunological data from administering the same composition in Goni *et al., Neuroscience* 133 (2005) 413–421, attached as Exhibit A. Specifically, Goni *et al*. demonstrate that following oral administration of *S. typhimurium* LVR01 expressing recombinant PrP protein, mice had significantly elevated levels of fecal (i.e., mucosal) anti-PrP IgA. *Goni et al.* at 416, Figure 4. Furthermore, Goni *et al.* demonstrate that plasma IgG anti-PrP antibodies (i.e., concomitant immunoglobulin in other bodily fluids) were generated following mucosal administration of the PrP composition. *Goni et al.* at 417, Figure 5. Moreover, Goni *et al.* demonstrate a correlation between mucosal IgA anti-PrP levels and a delay in the incubation period, thereby demonstrating that gut (mucosal) IgA is protective. *Goni et al*. at 417, Figure 6. Lastly, Goni *et al.* disclose that evidence of toxicity or autoimmune disease (as would be caused by Th1-type cytotoxic T lymphocyte mucosal immune responses) in vaccinated mice was not seen. *Goni et al.* at 419, middle of left column. Thus, Applicants respectfully submit that the claimed composition does indeed elicit a primarily Th-2-type immune response that is associated with a mucosal IgA humoral immune response and any concomitant immunoglobulin counterpart in other bodily fluids, and is not associated with a primarily Th-1-type cytotoxic T-lymphocyte response. See also further detailed immunological data showing that the above composition elicited mucosal IgA responses and concomitant systemic IgG in immunized mice, as well as showing complete (100%) protection from prion infection in mice that had good responses to the vaccine in Goni et al. *Neuroscience* (2008) 153:679–686, e.g., Figs. 2 and 3, attached as Exhibit B.

III. The Obviousness Rejections Should Be Withdrawn

Claim 1 remains rejected under 35 U.S.C. § 103(a) as being obvious over Krasemann *et al.* (*Journal of Immunological Methods*, 1996, Vol. 199, p. 109-118) (hereafter "Krasemann") in view of Sigurdsson *et al.* (*American Journal of Immunology*, 2002, Vol. 161, p. 13-17) (hereafter, "Sigurdsson").

Claim 20 and its dependent Claims 28, 51, and 52 remain rejected under 35 U.S.C. § 103(a) as being obvious over Krasemann in view of Sigurdsson as applied to Claim 1 and further in view of U.S. Patent 5,733,760 by Lu et al. ("Lu"), Chabalgoity et al. (*Vaccine*, 2001, Vol. 19, p. 460-469, in IDS of 11/18/2005) ("Chabalgoity"), and Grones and Turna (*Biochemical and Biophysical Research Communications*, 1995, Vol. 206, pp. 942-947) ("Grones").

Claims 3, 4, 22, 23, 45-46, and 53, which depend from Claim 1 or Claim 20, have been rejected under 35 U.S.C. § 103(a) as being obvious over Krasemann in view of Sigurdsson as applied to Claims 1 and 20 in view of Lu and Chabalgoity, and further in view of U.S. Patent Publication No. 2002/0194634 by Dunne et al. ("Dunne") and Benkirane et al. (*Journal of Biological Chemistry*, 1993, Vol. 268, p. 26279-26285, in IDS of 11/18/2005) ("Benkirane").

Claims 9, 10, and 56, which depend from Claim 1, have been rejected under 35 U.S.C. § 103(a) as being obvious over Krasemann in view of Sigurdsson as applied to Claim 1 in view of Lu and Chabalgoity, and further in view of Clements et al. (U.S. Patent No. 6,440,423) ("Clements"), and Kleanthous et al. (U.S. Patent No. 6,585,975) ("Kleanthous").

As Claims 1, 3, 4, 9-13, 15-19, 40 and 56 have been canceled, the rejection of those claims is rendered moot. With respect to Claim 20 and its dependent claims 22, 23, 28, 45, 46 and 51-53, Applicants respectfully traverse the rejection for obviousness, as discussed in detail below.

The present claims recite an immunogenic composition comprising an attenuated bacterium microorganism consisting of one of a *Shigella* strain and a *Salmonella* strain transformed with a vector capable of expressing a non-infectious, non-pathogenic mammalian prion protein selected from the group consisting of mouse, bovine, deer, elk, and sheep prion protein, wherein the composition is suitable for mucosal administration and, when administered mucosally to a mammal expressing an endogenous prion protein, elicits a primarily Th-2-type immune response against said endogenous prion protein of said mammal that is associated with a mucosal IgA humoral immune response and any concomitant immunoglobulin counterpart in other bodily fluids, and is not associated with a primarily Th-1-type cytotoxic T-lymphocyte response.

Neither Krasemann nor Sigurdsson disclose or suggest a *Shigella* or *Salmonella* strain transformed with a vector capable of expressing a *non-infectious, non-pathogenic* mammalian prion protein selected from the group consisting of mouse, bovine, deer, elk, and sheep prion protein.

Lu and Chabalgoity fail to cure the deficiency of Krasemann and Sigurdsson, because they do not teach or suggest any *Shigella* or *Salmonella* compositions expressing a *non-infectious, non-pathogenic* mammalian prion protein. Lu and Chabalgoity only disclose compositions expressing antigens derived from *infectious pathogenic* agents. See, e.g., Lu at col. 4, lines 47-49 (HIV antigen); Chabalgoity at page 466, 2nd col. ("live recombinant *Salmonella* that express heterologous antigens from other pathogens"). Furthermore, in contrast to the present claims, neither Lu nor Chabalgoity teaches or suggests any *Salmonella* compositions which, when administered mucosally to a mammal expressing an endogenous prion protein, elicit a primarily Th-2-type immune response that is not associated with a primarily Th-1-type CTL response. In fact, both Lu and Chabalgoity disclose that the *Salmonella* vectors induce Th-1 responses, even when administered mucosally. *See*, Lu at col. 4, lines 53-64. *See* also, Chabalgoity at page 466, 2nd col., last paragraph stating that "Using the *salmonella* delivery system for studies conducted in mice, it has been shown that the immune responses elicited are *biased to a Th1 profile*" (emphasis added).

In addition, Applicants respectfully submit that the only prion **protein**-containing composition disclosed in Krasemann is not an immunogenic composition that is *suitable for mucosal administration* as required by the present claims. Specifically, Krasemann (at p. 115) discloses that human prion protein (PrP) was synthesized by transcribing the PrP gene with T3-RNA polymerase and translating the transcripts in vitro in rabbit reticulocyte lysate in the presence of [^{35}S] methionine to radioactively label the resulting protein product. As evidenced by the Material Safety Data Sheet (MSDS) for ^{35}S, attached as Exhibit C, ^{35}S is dangerous and therefore not suitable for any type of *in vivo* administration, including mucosal administration, as required by the pending claims. Moreover, rabbit reticulocyte lysate contains RNAse inhibitor, which is specifically described by its manufacturer as not suitable for administration to humans or animals (see Exhibit D, bottom of first page).

The Examiner argues that Krasemann also discloses a composition containing DNA encoding prion protein that *was* used for *in vivo* administration, resulting in anti-PrP antibodies, and concludes that this is the evidence that Krasemann teaches generation of antibodies against prion protein. *Office Action* at 6. Applicants respectfully disagree and submit that Krasemann's composition is not capable of eliciting an immunoglobulin response against endogenous prion protein in a mammal expressing endogenous PrP, as presently claimed. As evidenced by Krasemann's own data and disclosure, the sera of PrP DNA immunized prion-gene positive mice (i.e., mice expressing endogenous prion protein) "did not show any reactivity against prion sequences in a peptide ELISA. They also failed to detect recombinant prion protein in immunofluorescence assays." *Krasemann* at 113, right column. Thus, Krasemann's DNA composition is not capable of eliciting an anti-PrP immunoglobulin response in a mammal *expressing endogenous prion protein*, and therefore fails to disclose a composition possessing each of the presently claimed properties.

Thus, for the reasons discussed above, none of the compositions disclosed by Krasemann, containing either prion protein or DNA, make obvious the presently claimed composition, and none of the secondary references cure the deficiency of Krasemann, even if combined.

As discussed in detail in response to the previous two Office Actions, Sigurdsson's CFA- and IFA-containing compositions did not induce an immune response that was sufficient to treat prionoses. The secondary references cited by the Examiner do not cure the deficiency of Sigurdsson, because none of them teach or suggest that Sigurdsson's CFA- and IFA-containing compositions could be administered mucosally without CFA or IFA to successfully induce a Th2-mediated mucosal immune response, since Sigurdsson's compositions were hardly effective with CFA and IFA. The understanding in the field at the time of the present invention was that it is extremely difficult to break tolerance to antigens regarded by the immune system as self antigens, such as e.g., endogenous prion proteins. Therefore, the skilled artisan would have had **no reason** to adapt Sigurdsson's composition for mucosal administration, e.g., using a *Shigella* or *Salmonella* vector as recited in the present claims. It is only with improper hindsight that the Examiner would determine that the skilled artisan would remove CFA from Sigurdsson's already hardly effective composition. Thus, Applicants respectfully submit that Sigurdsson fails to cure the deficiency of Krasemann or any of the other cited references.

Benkirane discloses that D-residues increase the antigenicity of antigenic peptides and lead to the generation of high levels of IgG3 antibodies. This reference does not disclose or suggest any of the other composition properties recited in the present claims and does not cure the deficiency of Krasemann or Sigurdsson.

Grones discloses *Shigella* transformed with heterologous plasmids, and discloses none of the other properties recited in the present claims. Grones therefore fails to cure the deficiency of Krasemann and Sigurdsson.

Dunne discloses generation of transgenic bovine and cervid animals comprising a transgene encoding mutant PrP polypeptides generated by site-directed mutagenesis (see, e.g., ¶ [0015]). Dunne expresses mutant PrP in *E. coli* pCR2.1 vectors and uses these vectors *in vitro* to generate transgenic embryos. This reference does not disclose any immunogenic composition comprising a wild-type PrP protein that is suitable for mucosal administration, and when administered mucosally to a mammal expressing an endogenous prion protein, elicits a primarily Th-2-type immune response against said endogenous prion protein that is associated with a

mucosal IgA humoral immune response and any concomitant immunoglobulin counterpart in other bodily fluids, and is not associated with a primarily Th-1-type CTL response. Dunne's compositions were not designed to be immunogenic, but rather were designed to generate transgenic embryos.

Taken together, even if combined, the cited references do not disclose or suggest the compositions recited in the present claims.

In light of the foregoing arguments, the present claims are not obvious over the citedreferences. Withdrawal of the rejection under 35 U.S.C. § 103(a) is respectfully requested.

CONCLUSION

In view of the above arguments and amendments, it is respectfully submitted that the present claims are now in condition for allowance and such action is earnestly solicited. If the Examiner believes that a telephone conversation would help advance the prosecution in this case, the Examiner is respectfully requested to call the undersigned attorney at (214)-760-6165.

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Respectfully submitted,

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